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doi:10.1093/humrep/dep423

Advanced Access publication on December 10, 2009

A fatal case of ovarian hyperstimulation syndrome with perforated duodenal ulcer

Sir,

Ovarian hyperstimulation syndrome (OHSS) is a disturbing complication in infertility treatment. OHSS treatments aim to reduce vascular permeability, and include antiprostaglandin, anti vascular endothelial growth factor (VEGF), dopamine agonist and inhibition of VEGFR-2

phosphorylation (SU5416) (Soares *et al.*, 2008). We wish to draw attention to a recent case of ours, a giant perforated duodenal ulcer, an extremely rare associated disorder of OHSS. Only one similar case has been reported previously (Uhler *et al.*, 2001). Psychological stress from infertility and IVF may be instrumental in inducing peptic ulcers (Reed, 2002), and therefore prophylactic treatment of stress ulcers is critical in hyperstimulation situations (Barletta *et al.*, 2002).

We recently treated a 30-year-old nulligravid woman with amenorrhea and infertility (>8 years). She had no history of serious clinical illness, clinical examination was normal; she had normal hysterosalpingography and slight galactorrhoea, ultrasonic pelvic examination showed a small uterus, endometrial diameter of 3 mm and normal ovaries. Laboratory data showed slightly increased serum level of prolactin (601 mIU/ml).

A treatment regime, Cabergoline 0.5 mg twice per week and human menopausal gonadotrophin (hMG) 225 IU per day for 6 days, was begun. Vaginal ultrasound at Day 7 showed numerous small follicles with the largest diameter of 13 mm. In order to prevent hyperstimulation syndrome, human chorionic gonadotrophin (hCG) administration was retarded for 4 days and she received only one ampoule 75 IU hMG every other day. In total, 20 hMG ampoules (18 + 2) were administered, and after 4 days 5000 hCG was injected. Three days after injection of hCG, patient was admitted in hospital with abdominal pain and vomiting. Blood examination showed WBC 14 900/ml, haemoglobin 14.5 g/dl, hematocrit 45.2%, platelet count 250 000/ml albumin 4 g/l, creatinine 1.5 mg/dl.

Abdominal ultrasound demonstrated large ovaries (12–13 cm) with numerous follicles and some fluid in the posterior cul-de-sac. One day after admission she was transferred to intensive care unit (ICU) because of cyanosis and severe abdominal pain. Peritoneal fluid was aspirated under abdominal ultrasound guide, which contained elevated protein (8 g/dl), WBC (2000/ml), RBC (2200/ml) counts. She developed upper mid abdominal pain on the seventh day, and her status continued to deteriorate. High fever appeared 2 days after ICU admission. Patient was intubated and mechanical ventilation started immediately. A laparotomy was performed to investigate cystic ovarian torsion or rupture of ovary. Little fluid was detected in abdomen, ovaries were large and very soft, the right ovary contained a yellowish fluid, and no rupture or torsion and no injured intestine was observed. A large fragment of the ovaries were removed and a pelvic drain was inserted. Three to four days after laparotomy large volume of yellow discharge from the abdominal drain was observed, and after opaque meal X-ray, duodenal perforation was diagnosed. A surprising, 3–4 cm, giant perforated duodenal ulcer in anterior wall of duodenum was observed in the second laparotomy. A large drain was inserted into the duodenum via the ulcer opening, and another one was left in the peritoneum close to the ulcer to collect the probable remaining secretions (Gupta *et al.*, 2005).

Despite broad spectrum antibiotic therapy, high fever continued 25 days after the operation. Forty eight days after arrival, a third laparotomy was performed but after 2 h the patient died.

In the final week, the patient developed symptoms of disseminated intravascular coagulation, hematuria and low platelet count.

To our knowledge, only one previous case of duodenal perforation with critical OHSS has been reported (Uhler *et al.*, 2001). This case thus poses the question; should stress ulcer and duodenal perforation be included in complications of OHSS or not?

Diagnosis and treatment were, in this case, delayed because the occurrence of a duodenal perforation was not initially considered for a number of reasons: (i) abdominal pain, large tender abdomen, tachypnea and tachycardia are the cardinal signs of OHSS, and it is very difficult to distinguish it from other acute abdomen causes especially duodenal perforation, and (ii) peritoneal fluids in both conditions are similar, and yellow in colour.

In our patient on the second day in ICU high fever appeared. High fever is an important symptom of duodenal perforation (Gupta *et al.*, 2005) but it may be a symptom of peritonitis caused from needle contamination or perforation of intestine in the time of ovum extraction or ascites aspiration. One case of OHSS and perforated appendicitis was reported in 2003 with high fever (Fujimoto *et al.*, 2002).

A multicentre study reviewing OHSS patients showed that febrile morbidity among severe and critical OHSS patients was remarkably high, affecting 83.3% of all patients (Abramov *et al.*, 1998).

Thus, accurate diagnosis is very complicated and, in this case, diagnosis was made on the basis of large quantity of discharge from her abdominal drain. Ovarian reduction surgery or partial oophorectomy (Amarin, 2003), such as that performed in this patient, is not recommended unless in a critical patient. Instead of wedge resection or partial oophorectomy, bilateral complete oophorectomy may be inevitable.

This letter highlights the importance of physician attention and careful monitoring of patients after ovarian stimulation for early detection of any possible complication, particularly patients with OHSS.

We propose that duodenal perforation should be considered as one of the associated complications of OHSS, and suggest that clinicians pay particular attention to this when, despite surgery and intensive medical care, the patient does not stabilize and abdominal pain continues. In our case, had we known of this complication, we might have saved the life of this patient.

Acknowledgements

The authors would like to thank Farzan Institute for Research and Technology for technical assistance.

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doi:10.1093/humrep/dep434

Advanced Access publication on December 9, 2009

Does the estradiol level on the day of human chorionic gonadotrophin have an impact on pregnancy rates in patients treated with rec-FSH/GnRH antagonist?

Sir,

We read with interest the article of Kyrou *et al.* (2009). The authors prospectively evaluated the impact of E₂ exposure on clinical pregnancy rates (PR) in 207 patients undergoing assisted conception treatment with GnRH antagonist protocol. Categorising patients according to E₂ percentiles instead of arbitrary chosen cut-off E₂ levels adds value to the design of the study. At the end, the authors concluded that elevated E₂ levels could have a deleterious effect on endometrial receptivity. However, it is not clear how the authors came to this conclusion based on their results. Their analyses revealed that neither implantation rates (IR) nor PR differed according to the E₂ percentile category of the patients assessed. Although a subgroup analysis of their data revealed statistically higher E₂ levels among non-pregnant cases in high responders, the number of patients are too low (51 patients) to draw a conclusion. Moreover the subgroups they analysed were not homogenous such as more ICSI cycles and higher progesterone levels were observed in the non-pregnant hyperresponder group. Therefore, we assume that authors' null hypothesis should have been 'elevated E₂ levels were better correlated with higher PR' and their null hypothesis was rejected because of the results achieved in the current study.

The authors discussed several articles addressing elevated E₂ levels and its impact on endometrium and clinical outcome. On the other hand, they did not recognise recent relevant articles (Bahceci *et al.*, 2006; Ulug *et al.*, 2006). These two studies retrospectively evaluated more than 5000 GnRH agonist down-regulated ICSI–embryo transfer cycles according to the E₂ percentiles on the day of hCG and did not find adverse impact of high E₂ levels on the clinical outcome in terms of IR, PR and both subclinical and clinical pregnancy losses. Hence inferior PR were correlated to lower E₂ levels. It is of note that severe OHSS due to exaggerated E₂ levels should be ruled out as it was an exclusion criteria in the current study.